UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,922	08/31/2001	Vassilios Papadopoulos	1941.017US1	9599

21186 7590 12/26/2007

SCHWEGMAN, LUNDBERG & WOESSNER, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
DANG, IAN D	

ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
12/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/623,922	PAPADOPOULOS ET AL.	
	Examiner	Art Unit	
	IAN DANG	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/03/2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-9,20-26,29,30,32 and 39* is/are pending in the application.

4a) Of the above claim(s) *9,21-26,29,30,32 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-8 and 20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,2,4-9,20-26,29,30,32 and 39* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/03/2007,10/24/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10/03/2007 has been entered in full. Claims 3, 10-19, 27-28, 31, and 33-38 have been cancelled and claims 1, 5, and 20 have been amended. Claim 39 has been added.

This application contains claims 9, 20-26, 29, 30, and 32 drawn to an invention nonelected with traverse in the reply filed on 04/25/2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Newly submitted claim 39 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: SEQ ID NO:27 has a different amino acid sequence from SEQ ID NO:26.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claim 39 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 2, 4-8, and 20 are pending and under examination.

Priority

Applicant's response and arguments at page 6 of the response filed on 10/03/2007 are persuasive. The claims in the pending application receive the benefit of the 60/077,753 application filed on March 12, 1998.

Rejection Withdrawn

35 USC § 101

Applicant's response and amendments made to claim 1 filed on 10/03/2007 have overcome the rejection of claims 1-8 and 20 under 35 USC § 101. The rejection of claims 1-8 and 20 under 35 USC 101 has been withdrawn.

35 USC § 102

Applicant's response, amendments made to claim 1, and cancellation of claim 3 filed on 10/03/2007 have overcome the rejection of claims 1-8 and 20 under 35 USC § 102(b). Garnier teaches a consensus sequence present from amino acid residues 149 to 156 of the benzodiapenzine receptor polypeptide (Figure 1, page 204). The consensus sequence of Garnier is comprised within a larger sequence. However, the rejection is withdrawn because Applicant amended claim 1 to recite "consisting of" language. The rejection of claims 1-8 and 20 under 35 USC 101(b) has been withdrawn.

35 USC § 112, First paragraph (Written Description and Enablement)

Applicant's cancellation of claim 3 filed on 10/03/2007 has overcome the rejection of claim 3 under 35 USC § 112, First Paragraph. The rejection of claim 3 under 35 USC 112, First Paragraph has been withdrawn.

Rejection Maintained

Claim Rejections - 35 USC § 112 (Written Description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-8 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis of this rejection is set forth for claims 1-8 and 20 at page 5 of the previous Office action of 02 July 2007.

The rejection of claims 1, 2, 4-8 and 20 is maintained. Applicant's response and arguments filed on 10/03/2007 have been fully considered but they are not persuasive.

At page 7 of the response, Applicants argue that the claims recite common structural attributes identifying the members of the genus, i.e., Z-$(X)_{0-5}$-Try-$(X)_{0-5}$-B, wherein Z is a neutral hydrophobic amino acid, B is a basic amino acid, and X is any amino acid. The specification discloses neutral hydrophobic amino acids and basic amino acids at page 10, lines 14-20. Numerous (19) exemplary cholesterol recognition/interaction amino acid sequences are disclosed in Table 1. Further, the specification discloses substitutions that altered cholesterol recognition of a particular cholesterol recognition/interaction amino acid sequence (see claim 29).

Applicant's arguments have been fully considered but are not found persuasive. To provide adequate written description and evidence of possession of claimed genus, the specification must provide efficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure/function correlation, and other identifying characteristics. Accordingly, in the absence of sufficient recitation of distinguishing structural/physical and identifying characteristics, the specification does not provide adequate written description of the claimed genus.

The claimed cholesterol recognition/interaction amino acid consensus sequence recited in claim 1 does not satisfy the written description requirement because Applicant recites general characteristics regarding the structural attributes of a cholesterol recognition/interaction amino acid consensus sequence without any sufficient recitation of distinguishing structural/physical and identifying characteristics of the cholesterol/interaction amino acid consensus sequence. For instance, the claims recite structural characteristics a cholesterol recognition/interaction amino acid consensus sequence consisting of SEQ ID NO:26, but it does not disclose any identifying structural characteristics of the consensus sequence associated with the functional biological activity of any consensus sequence. While Applicant discloses exemplary cholesterol recognition/interaction amino acid sequences are disclosed in Table 1 (page 10), Applicant has not provided any specific identifying structural characteristics so that one skilled in the art can correlate with a distinct biological function. At page 13 of the specification, Applicant teaches that the presence of the cholesterol interaction/ recognition consensus sequence in the proteins listed in Table 1 signifies the likelihood that the proteins interact with cholesterol and provides insight into how these proteins accomplish their functions in concert with cholesterol and how to alter these functions (lines 1-7). However, the specification does not provide sufficient teachings correlating the structure of the cholesterol recognition/interaction amino acid consensus sequence consisting of SEQ ID NO:26 with its biological function, so that one skill in the art can identify the claimed cholesterol recognition/interaction amino acid consensus sequence of the instant application.

In addition, there is no description of the conserved regions, which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, the prior art does not provide compensatory structural or correlative

teachings sufficient to enable one of skill to isolate and identify the cholesterol recognition/interaction amino acid consensus sequence consisting of SEQ ID NO:26 encompassed by the claims. Thus, no identifying characteristics or properties of the instant cholesterol recognition/interaction amino acid consensus sequence consisting of SEQ ID NO:26 are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 1, 2, 4-8, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands, 8USPQ2d, 1400 (CAFC 1988) page 1404, the factors to be considered in determining whether a disclosure would require undue experimentation include: (1) Nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the breath of the claims, (7) the quantity of experimentation needed, (8) relative skill of those in the art.

At page 7 of the response, Applicants argue that Applicants need not teach or suggest the mechanism by which a protein having a cholesterol recognition/interaction sequence binds cholesterol, to satisfy the enablement requirement of § 112(1). Similarly, even if the strength and specificity of the interaction of a protein having a cholesterol recognition/interaction sequence with cholesterol can vary (Li et al.) that is irrelevant to whether Applicant has taught how to make and use the claimed peptides that include a cholesterol recognition/interaction amino acid consensus sequence. Finally, Applicants cite numerous case laws to overcome the enablement rejection.

Applicant's arguments have been fully considered but are not found persuasive. As disclosed at pages 10-11 of the previous Office action, the cholesterol recognition/interaction amino acid consensus sequence consisting of VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide is not predictable for all possible cholesterol recognition/interaction amino acid consensus sequences consisting of SEQ ID NO:26. Thus it would require undue experimentation by one skill in the art to make/use the cholesterol recognition/interaction amino acid consensus consisting of SEQ ID NO:26 without sufficient disclosure in the specification.

It is noted that at page 8 of the response, Applicant cites pertinent case law reviewing the legal standard of enablement. The Examiner takes no issue with Applicant's general comments regarding the legal standard for enablement.

It is noted that after further consideration of the instant specification, the Examiner has rejected all the claims under 36 U.S.C. § 112, first paragraph (total lack of enablement) rather than a scope of enablement, as presented in the previous Office Action 02 July 2007.

Nature of the invention and breath of the claims

The invention is drawn to the cholesterol recognition/interaction amino acid consensus sequence consisting of Z-$(X)_{0-5}$-Tyr-$(X)_{0-5}$-B (SEQ ID NO:26) of the peripheral-type benzodiazepine receptor (PBR) polypeptide. The invention is broad because the recitation of claims 1-8 and 20 encompasses a large number of polypeptides due to the numerous combinations of amino acids for each position of the consensus sequence. Specifically, the specification teaches that the present invention relates to a minimum amino acid sequence specific for recognition/interaction with cholesterol, namely the amino acid sequence -Z- $(X)_{0-5}$-Y- $(X)_{0-5}$-Q wherein Z represents a neutral and hydrophobic amino acid, such as Leucine, Valine Alanine, Isoleucine, Methionine, Phenylalanine and Tryptophan, Y represents a neutral and polar amino acid, such as Tyrosine, Threonine, Serine, Glycine, Glutamine, Cysteine, Asparagine, Q represents a basic amino acid such as Arginine, Lysine, or arginine, and X represents any amino acids selected from the group consisting of Alanine (Ala, A) , Arginine (Arg, R) , Asparagine (Asn, N), Aspartic acid (Asp, D), Cystein (Cys, C), Glutamine (Gln, Q), Glutamic acid (Glu, E), Glycine (Gly, G), Histidine (His, H), Isoleucine (Ile, I), Leucine (Leu, L), Lysine (Lys, K), Hethionine (Met, M), Phenylalanine (Phe, F), Proline (Pro, P), Serine (Ser, S), Threonine (Thr, T), Tryptophan (Trp, W), Tyrosine (Tyr, Y), and Valine (Val, V) (page 10, lines 9-29).

Unpredictability and state of the art

The state of the art for the cholesterol recognition/interaction amino acid consensus sequence comprising VLNYYNWR (SEQ ID NO:5) of peripheral-type benzodiazepine receptor (PBR) is not predictable for a cholesterol recognition/interaction amino acid consensus sequence consisting of SEQ ID NO:5 or SEQ ID NO:26.

As indicated at page 9 of the previous Office action (mailed 07/02/2007), the instant cholesterol recognition/interaction amino acid consensus sequence for PBR has been characterized in the specification and in several references. For instance, Lacapere et al. (2003, Steroids, Volume 68, pages 569-585) recite that the characterization of the consensus sequence is well characterized for PBR and has been identified for other proteins. In addition, Lacapere et al. teach that the deletion of the C-terminus of PBR (delta 153-169) drastically reduced cholesterol uptake (70%), although it retained ability to bind PK 11195 ligand. Site directed mutagenesis in this 153-169 region enabled the characterization of amino acids involved in cholesterol binding. A CRAC sequence has been determined (ATVLNYYVWRDNS) and this amino consensus pattern has been observed in several other proteins known to interact with cholesterol (page 577, right column, 2nd paragraph).

However, the state of the art is silent regarding the biological functions of the cholesterol recognition/interaction consensus sequence *consisting* of SEQ ID NO:5 or SEQ ID NO:26. In addition, the art does not disclose if these small peptides can act as a cholesterol recognition/interaction consensus.

The amount of direction or guidance present

Applicants' disclosure is limited to cholesterol recognition/interaction amino acid consensus sequence VLNYYNWR (SEQ ID NO:5) of the peripheral-type benzodiazepine receptor (PBR) polypeptide. The specification provides numerous examples (Figures 1, 3, and 4) and recites that the carboxy terminal of PBR is responsible for the interaction and subsequent uptake of cholesterol.

However, the specification does not provide any guidance or direction regarding the biological functions of the cholesterol recognition/interaction consensus sequence consisting of

SEQ ID NO:5 or SEQ ID NO:26. While the teachings of the specification for cholesterol consensus apply to SEQ ID NO:5 as it is comprised within the larger amino acid sequence of PBR, these specificities and biological activities for the cholesterol recognition/interaction amino acid consensus of PBR may not be applicable to the polypeptides consisting of amino acid sequences disclosed in Table 1 (page 12). Specifically, the specification recites that the presence of the cholesterol interaction/recognition consensus sequence in the proteins listed in table 1 signifies the likelihood that the proteins interact with cholesterol and provides insight into how these proteins accomplish their functions in concert with cholesterol and how to alter these functions (page 13, lines 1-7).

Working Examples

Although Applicants have provided several examples for the characterization of the biological activity for the cholesterol sequence consensus of PBR, the specification does not provide any working examples for the biological activity of the consensus sequence consisting of SEQ ID NO:5. There are no examples disclosing the biological activities of a cholesterol recognition amino acid consensus sequence consisting of SEQ ID NO:5 or SEQ ID NO:26. Specifically, the examples disclose the biological functions of the consensus sequence comprising SEQ ID NO:5 as it is comprised within PBR (see Figures 1 and 3) and several proteins comprising a cholesterol recognition/interaction amino acid consensus pattern Table 1 (page 12).

The quantity of experimentation needed

A large amount of experimentation would be required to be able to practice the invention commensurate in scope with the claims because the claims and specification do not provide any

identifying structural and functional characteristics associated with a biological activity for an isolated cholesterol recognition/interaction amino acid consensus sequence. Applicant has also provided little or no guidance beyond the mere presentation of sequence data to enable the skilled artisan to determine, without undue experimentation, the positions in the cholesterol recognition/interaction amino acid consensus consisting of SEQ ID NO:26 which are tolerant to change (e.g. such as by amino acid substitutions, additions or deletions) and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Undue experimentation would be required of the skilled artisan to generate the large number of derivatives recited in the claims and screen the same for the desired activity. One skilled in the art cannot predict that the derivatives of the cholesterol recognition/interaction amino acid consensus consisting of SEQ ID NO:26 will have the same functional activities as the cholesterol recognition/interaction amino acid consensus comprising SEQ ID NO:5 (as it is comprised with PBR) since deletions, substitutions, and additions of amino acid residues can often destroy activity of a protein.

Conclusion

No claim is allowed.

Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IAN DANG whose telephone number is (571)272-5014. The examiner can normally be reached on Monday-Friday from 9am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ian Dang
Patent Examiner
Art Unit 1647
December 19, 2007

/Bridget E Bunner/
Primary Examiner, Art Unit 1647